## Remarks

Claims 15, 16, 21-24 and 26-27 are currently under consideration. Claims 15, 16 and 21 have been amended to depend from Claim 22. Claim 22 has been amended as suggested by the Examiner. The amended Claims find support at Claims 1-14 and 17-20, which have been cancelled without prejudice. Claims 24 and 26 find further support at page 23, line 3. Claims 23 and 27 find further support at page 23, line 8. A new matter rejection has been lodged against the previously submitted amendment to text at the paragraphs bridging pages 22-23 and pages 23-24. The text has been amended to update drug names and source information. No new drugs are added.

### Restriction Requirement

The Examiner had stated that Claims 1-14 and 17-20 and now 22-27 are free of the prior art, at least with respect to the use of a specific two-drug combination in the claimed method. The applicants request that the claims be searched with respect the class of drugs (antiretroviral drug therapies) involved. This case was filed in 2001, and any nearly contemporaneous research articles should be available by now.

### Objections to the Specification – New Matter

The Examiner states that the amendment filed 3-11-04 is objected to under 35 U.S.C. 132 because it is said to introduce new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material that is said to be not supported by the original disclosure is as follows: the paragraph bridging pages 22-23 and the paragraph bridging pages 23-24. The Examiner states that the Applicant is required to cancel the new matter in the reply to this Office Action.

### Response

The industry is very active at this time, and this information is offered for the purpose of facilitating search by others. For example, Gilead Sciences (formerly, Gilead

pharmaceuticals) uses the trade name Preveon® for a drug known variously as adefovir, adefovir dipioxil and PMEA, the trade name Viread® for the drug know as tenofovir, tenofovir DF and PMPA; Glaxo Wellcome is now GlaxoSmithKline; efavirenz (Sustiva®) was once owned by DuPont and is now owned by Bristol-Myers Squibb; lubocavir developed safety issues and is no longer available, and so has been deleted. Similarly, with respect to the paragraph bridging pages 23-24, Nelfinavir (Viracept®) has been available overseas from Roche, but is available from Auguoron in the US now. GW141, formerly available from Glaxo Wellcome/Vertex, is no longer available and has been deleted. Tipranavir, formerly available from Pharmacia & Upjohn, is now available from Boehringer. An alternate generic drug name, atazanavir, and a trade name, Reyataz® have come into use for a Bristol-Myers Squibb material, BMS 232632. All of the original materials were cited in the original specification. No new matter is added by any of these amendments. The text amendments are supported by the previously submitted list of drugs from AidsMeds.com and publicly available drug information sheets. It would seem that if updated information with respect to patent application status is required for the convenience of the public, that a parallel update with respect to drug names and sources should be encouraged. In light of these remarks, if the Examiner renews this objection, the applicants will re-amend the application.

**Claim Objections - 35 USC § 112**

New claims 22 and 25 have been objected to because they are said not to clearly set forth the replication of the retrovirus is suppressed. While the Examiner admits that claims 22 and 25 state that the host is infected with a retrovirus and that viral replication is suppressed, the viral replication being suppressed could be any virus. The Examiner states that the claim should more clearly state that replication of the retrovirus is suppressed.

Similarly, new claims 22 and 25 have been objected to because they are said not to clearly set forth the gene delivery complex comprises two elements, the DNA and mannosylated polyethylenimine. The Examiner recommends that the two steps may be

marked i) and ii) and the two elements of the gene delivery complex used in step ii) may be marked a) and b).

**Response**

In response, the claims have been amended as suggested by the Examiner.

**Claims 22-27**

The Examiner admits that administering an antiretroviral drug therapy comprising ddI and Indinavir until viral replication is effectively suppressed is considered enabled because Finzi taught administering a reverse transcriptase inhibitor and a protease inhibitor suppressed viral replication (Finzi et al. Science. Nov. 14, 1997, Vol. 278, pg 12951300). The Examiner states that Claims 22-27 require administering DNA encoding an immunogenic retroviral protein after administering the antiretroviral drug therapy. The sole disclosed purpose for administering DNA encoding an immunogenic retroviral protein is to induce an immune response against a retroviral protein that is therapeutic (pg 2, lines 14-19). Therefore, the Examiner takes the position that the step of administering DNA encoding an immunogenic retroviral protein to obtain a therapeutic immune response against the "immunogenic retroviral protein". However, the Examiner states that the specification does not enable using DNA encoding an immunogenic retroviral protein to induce a therapeutic immune response against a retrovirus in a host.

**Response**

Use of the present invention, and a therapeutic response, is described in the application in Example 13.

**Claims 22-27, cont'd**

According to the Examiner, Claims 22-27 are not enabled because the structure of the DNA encoding an immunogenic retroviral protein that provides a therapeutic immune response against the retroviral protein is not enabled. The Examiner states that the state of the art at the time of filing was that the combination of vector, promoter, route of administration, level of expression and target tissue required to obtain a therapeutic or prophylactic effect using gene therapy was unpredictable. Miller of record (1995, FASEB

J., Vol. 9, pages 190-199) is said to review the types of vectors then available for in vivo gene therapy, and conclude that "for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances ... targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1). Deonarain of record (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) is said to indicate that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain is said to review new techniques under experimentation in the art that show promise but state that such techniques are even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma of record (Sept. 1997, Nature, Vol. 389, pages 239-242) is said to review vectors known in the art for use in gene therapy and discuss problems associated with each type of vector. The teachings of Verma are said to indicate a resolution to vector targeting has not been achieved in the art (see entire article). Verma is also said to teach that appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3). Crystal of record (1995, Science, Vol. 270, page 404-410) is said to review various vectors known in the art and indicate that "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (page 409).

The Examiner says that the state of the art regarding treating retroviral infection was unpredictable. Stricker of record (Medical Hypotheses, June 1997, Vol. 48, pages 527-9) is said to teach that attempts to develop a vaccine against HIV have been unsuccessful because HIV vaccines do not neutralize HIV (pg 527, last paragraph through all of pg 528). The Examiner concludes that, overall, a lack of understanding about protective immunity to HIV in humans, the sequence variability of HIV and the rapid

replication of HIV contribute the ineffectiveness of vaccines against HIV (Bangham of record, Nov. 29, 1997, Lancet, Vol. 350, pages 1617-1621 - page 1617, top of col. 1).

The Examiner notes that the present specification teaches a complex comprising i) manosylated PEI and ii) DNA encoding an immunogenic HIV protein operably linked to a promoter, and also that administration of the complex to a host after drug therapy was followed by an increase in CD4 cells then a decrease in CD4 cells (pg 53).

**Response**

The application shows more than CD4 results. It showed reduced viral replication, that is, a reduction in the rate of viral rebound when drug treatment was stopped after vaccination (page 53, lines 22-27; Fig. 14).

**Claims 22-27, cont'd**

The Examiner states that the specification does not provide adequate guidance for one of skill to use a gene delivery complex comprising "foreign genetic material" as a "therapeutic genetic immunization" as claimed. The Examiner says that the results described in the specification are not considered therapeutic because the overall result does not result in a net increase in CD4 cells; that it cannot be concluded that the gene complex caused the initial increase in CD4 cells because the experiment did not include controls, that is, animals that did not receive drug therapy or the gene complex. The Examiner also states that the specification does not provide adequate guidance indicating the increase in CD4 was caused by the gene complex - the drug therapy could have caused the increase in CD4. The Examiner says that the specification did not teach treating animals that were already infected or challenging the animals after they were given DermaVir. The Examiner continues that, for administration of foreign genetic material to be a "therapeutic genetic immunization", the specification must overcome the unpredictability in the art by adequately describing the structure of the "foreign genetic material" used, the dosage and route of administration that results in a therapeutic effect or "immunization." The Examiner concludes that, without such guidance it would require one of skill in the art undue experimentation to overcome the unpredictability in the art

regarding gene therapy and retroviral therapy to determine the combination of elements required to obtain a therapeutic or prophylactic effect against retroviral infection using "foreign genetic material, and so, the specification does not enable "therapeutic genetic immunization" using a gene delivery complex comprising "foreign genetic material" as claimed.

**Response**

In response, the Claims have been amended as suggested by the Examiner. Further, the text of the application contains evidence of unexpected therapeutic efficacy in Example 13, see especially page 53, lines 28-31.

**Claim Objections 1-14 and 17-20 under 35 USC § 112**

Claims 19 and 20 were said to be objectionable for containing the trademark/trade name delavirdine, abacavir, adefovir, nevirapine, efavirenz, lubocavir, PMPA, PMEA, indinavir, saquinavir, ritonavir, nelfinavir, and GW41. To the extent that some of these generic drug names (none are trade names or trademarks) are included in the present claims, the following remarks are offered to facilitate examination.

**Response**

The amended Claims use generic or established names for drugs, not trademark/tradenames. Due to their length and complexity, the chemical names of the referenced compounds are not well-known, and are not used for searching the literature. As a result, Congress has required that, if a prescription drug has an established name, it must be displayed with the trade name or trade mark on the label. (Sec. 502(e) of the Food and Drug Act and 21 CFR 202.1) and cross-references between the trade names and established are readily available (copies enclosed with previous amendment). The better policy on the part of the USPTO (and the general rule) is to use the established name for the drug in the claims, when this will facilitate searching. The applicants have amended the claims where a different name has become established for a new drug, and the text of the application has been amended in parallel, as well as to update source information.

The web pages enclosed with the previous amendment support the amendments. None of these amendments add new matter to the specification.

The applicants are willing, if the Examiner so requires, to insert the chemical names for each of these materials into the Claims along with the established names, but they respectfully submit that this will make the claims more, rather than less, obscure.

To take just one example, delavirdine has a chemical name 1-(3-((1-Methylethyl)amino)-2-pyridinyl)-4-((5-((methylsulfonyl)amino)-1H-indol-2-yl)carbonyl)piperazine.

**Examiner's Conclusion**

The Examiner has concluded that Claims 1-14 and 17-20, and now 22-27 are free of the prior art because the prior art did not teach or suggest administering ddI and Indinavir until viral replication is effectively suppressed, and then administering a gene delivery complex as claimed. Finzi et al. (Science. Nov. 14, 1997, Vol. 278, pg 1295-1300) are said to have taught administering reverse transcriptase inhibitors and protease inhibitors to HIV patients. However, the Examiner admits that Finzi et al. did not relate to administering DNA encoding the marker protein luciferase to the brain of mice as taught by Boussif et al (PNAS, Aug. 1995, Vol. 92. pg 7292-7301) of record, administering DNA encoding a marker protein to cells in vitro as taught by Zanta et al. (Bioconjugate Chem. 1997. Vol. 8. pg 839-844) of record, administering DNA encoding a marker protein to cells in vitro as taught by Behr et al. (US Patent 6,013,240) of record, or administering virus encoding integrase-defective HIV to cells in vitro as taught by Cara et al. (Virology, 1995, Vol. 208, pg 242-248). The following references have also been reviewed: Lori, Science, 1994, Vol. 266, pg 801-805; Lori, AIDS Res. Hum. Retrovir., 1997. Vol. 13, pg 1403-1409; Lori, AIDS Res. Hum. Retrovir., 1995, Vol. 11, pg 1149-1151; Hollinshead, US Patent 5,747,526;

Malley US Patent 5,521,161 -,

Malley, US Patent 5,736,526-,

Lin, US Patent 5,719,132;

Lori, US Patent 6,046,175

Malley, US Patent 6,093,702;

Lori, US Patent 6,194,390 ;

Critchfield, US Patent 6,274,611;

Lisziewicz, US Patent 6,114,312;

Lisziewicz, US Patent 6,251,874;

Lisziewicz, US Patent 5,977,086.

**Response**

The applicants thank the Examiner for this candid assessment and thorough search of the prior art, and asks for a wider search of the prior art to include the claimed classes and drugs.

**Double Patenting**

**Claims 1-14 and 17-20 over USPN 6,420,176**

Claims 1-14 and 17-20 have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-14 of U.S. Patent No. 6,420,176 in view of the disclosure of 6,420,176. The Examiner points out that the claims of '176 are directed toward a gene delivery complex comprising DNA encoding an immunogenic protein operably linked to a promoter and mannosylated polyethylenimine. The Examiner admits that the claims of '176 do not require administration as required in the instant claims or administration of antiretroviral drug therapy, but adds that MPEP 804 states the specification may be used as a dictionary to learn the meaning of a term in the patent claim. In this case, the Examiner says that one of skill would look to the specification to determine the asserted utility of the product. The disclosure taught administering the gene delivery complex after suppressing viral replication using antiretroviral drug therapy (col. 12, lines 11 -51, see especially lines 2027). Thus, the Examiner concludes that it would have been obvious to one of ordinary skill in the art at

the time the invention was made to administer the gene delivery complex in combination with drug therapy as claimed.

**Response**

The applicants note the present application is a continuation-in-part of the cited patent, which disclosed a potential pattern of treatment that had not yet been tried: at Col. 12, line 19 the patent reads "**If** the replication of the wild-type virus can be suppressed either before the immune system is substantially damaged or long enough to allow the immune system to recover, the vaccine of the present invention can be used to strengthen the immune system's ability to recognize the new variants of the virus..." This passage might make the experiments reported in the present application obvious-to-try, but obvious-to-try is not the standard for patentability, and the present application is based on surprising additional results. The experiments reported in the present application were originally designed as part of a safety study, and were not expected to yield a therapeutic result. The new disclosure in Example 13, page 53, lines 28-31 states "The unexpected therapeutic efficacy of DermaVir$_{SHIV}$ in animals at a late stage of the disease reveals a previously unsuspected capacity of the host to respond to vaccination...." Thus the present invention goes beyond the disclosure of the parent because it does not require early treatment ("before the immune system is substantially damaged") or extended antiretroviral treatment ("if... wild-type virus can be suppressed ... long enough to allow the immune system to recover...." This is extremely important, as it means that this method of vaccination is likely to be applicable to large classes of patients that were not thought to be amenable to such treatment due to the heavily documented, extensive immune system damage cause by HIV infection.

**Claims 1-14 and 17-20 over copending App. No. 10/081922**

Claims 1-14 and 17-20 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the claims of copending Application No. 10/081922. Although the Examiner admits that the

conflicting claims are not identical, he takes the position that they are not patentably distinct from each other because they allegedly overlap in scope. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

**Response**

The cited application is a division of USPN 6,420,176, cited above, and is distinguished on the same basis.

**Conclusion**

For all the above amendments and reasons is respectfully submitted that the Claims are in condition for allowance. Favorable consideration is solicited.

Respectfully Submitted,

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